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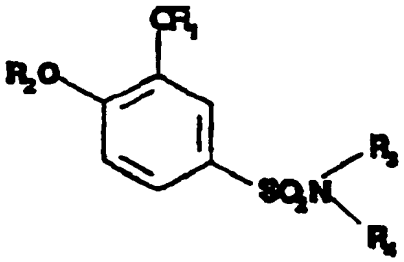
(54) Title: 3,4-DISUBSTITUTED-PHENYLSULPHONAMIDES AND THEIR THERAPEUTIC USE



(i)

(57) Abstract

3,4-Disubstituted benzenesulphonamides of general formula (i) in which R_4 represents a 5-or 6-membered saturated or unsaturated carbocyclic or heterocyclic ring to which ring is fused an aryl, hetereoaryl, carbocyclic or heterocyclic ring, in which either or both rings may optionally be substituted, and the other substituents are as defined in Claim 1, have therapeutic utility via phosphodiesterase IV inhibition.

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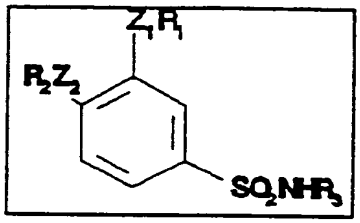
3,4-DISUBSTITUTED-PHENYLSULPHONAMIDES AND THEIR THERAPEUTIC USE

Field of the invention

The present invention relates to novel sulphonamide compounds and pharmaceutically acceptable salts thereof, processes for their production and their formulation and use as pharmaceuticals.

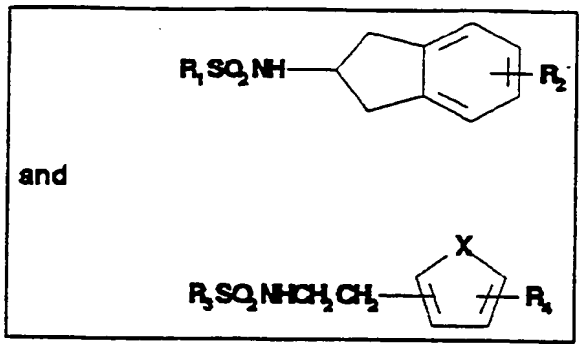
Description of the prior art

International Patent Application WO 94/02465 discloses inhibitors of phosphodiesterase IV and TNF including sulphonamides of formula:-



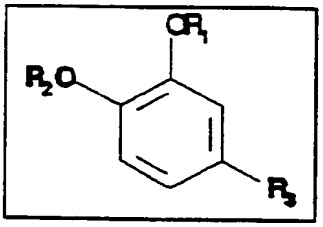
wherein R^1 is alkyl, alkenyl, cycloalkyl, cycloalkenyl, cyclothioalkyl, or cyclothioalkenyl ; R^2 is lower alkyl; R^3 is aryl or heteroaryl; Z^1 and Z^2 are independently oxygen or sulphur. The only sulphonamide exemplified is N-(2-chlorophenyl)-3-cyclopentyloxy-4-methoxybenzenesulphonamide.

European Patent Application 0 306 846 discloses sulphonamides of formula:-



as thromboxane A_2 antagonists. European Patent Application 0589 037 discloses structures similar to the above also as thromboxane A_2 antagonists.

United States Patents 5, 283, 352 and 4, 963, 590 disclose compounds of formula



in which R_3 may be sulphonamide, as catechol-O-methyl transferase inhibitors.

Phosphodiesterases regulate cyclic AMP concentrations. Phosphodiesterase IV has been demonstrated to be a principal regulator of cyclic AMP in respiratory smooth muscle and inflammatory cells. [See Torphy and Creslinski, Molecular Pharmacology 37, 206, (1990); Dent et al British Journal of Pharmacology, 90 163p (1990)]. Inhibitors of phosphodiesterase IV have been implicated as being bronchodilators and asthma-prophylactic agents and as agents for inhibiting eosinophil accumulation and the function of eosinophils. [See for example Gembycz and Dent, Clinical and Experimental Allergy 22 337 (1992)] and for treating other diseases and conditions characterised

by, or having an etiology including, morbid eosinophil accumulation. Inhibitors of phosphodiesterase IV are also implicated in treating inflammatory diseases, proliferative skin disease and conditions associated with cerebral metabolic inhibition.

Excessive or unregulated production of Tumour Necrosis Factor (TNF), a serum glycoprotein, has been implicated in mediating or exacerbating a number of diseases including rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions; sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoidosis, bone resorption diseases, reperfusion injury, graft vs. host reaction, allograft rejections, fever and myalgias due to infection, such as influenza, cachexia secondary to infection or malignancy, cachexia secondary to human acquired immune deficiency syndrome (AIDS), AIDS, ARC, (AIDS related complex), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis, or pyresis, in addition to a number of autoimmune diseases, such as multiple sclerosis, autoimmune diabetes and systemic lupus erythematosis.

AIDS results from the infection of T lymphocytes with Human Immunodeficiency Virus (HIV). At least three types or strains of HIV have been identified, i.e., HIV-1, HIV-2 and HIV-3. As a consequence of HIV infection, T-cell mediated immunity is impaired and infected individuals manifest severe opportunistic infections and/or unusual neoplasms. HIV entry into the T lymphocyte requires T lymphocyte activation. Viruses such as HIV-1 or HIV-2 infect T lymphocytes after T cell activation and such virus protein expression and/or replication is mediated or maintained by such T cell activation. Once an activated T lymphocyte is

infected with HIV, the T lymphocyte must continue to be maintained in an activated state to permit HIV gene expression and/or HIV replication.

Cytokines, specifically TNF, are implicated in activated T-cell mediated HIV protein expression and/or virus replication by playing a role in maintaining T lymphocyte activation. Therefore, interference with cytokine activity such as by inhibition of cytokine production, notably TNF, in an HIV-infected individual aids in limiting the maintenance of T cell activation, thereby reducing the progression of HIV infectivity to previously uninfected cells which results in a slowing or elimination of the progression of immune dysfunction caused by HIV infection. Monocytes, macrophages, and related cells, such as Kupffer and glial cells, have also been implicated in maintenance of the HIV infection. These cells, like T cells, are targets for viral replication and the level of viral replication is dependent upon the activation state of the cells. [See Rosenberg et al, The Immunopathogenesis of HIV Infection, Advances in Immunology, Vol. 57, (1989)]. Monokines, such as TNF, have been shown to activate HIV replication in monocytes and/or macrophages [See Poli et al, Proc. Natl. Acad. Sci., 87:782-784, (1990)], therefore, inhibition of monokine production or activity aids in limiting HIV progression as stated above for T cells.

TNF has also been implicated in various roles with other viral infections, such as the cytomegalovirus (CMV), influenza virus, adenovirus, and the herpes virus for similar reasons as those noted.

TNF is also associated with yeast and fungal infections. Specifically Candida albicans has been shown to induce TNF production in vitro in human monocytes and natural killer cells. [See Riipi et al., Infection and Immunity, 58(9):2750-54, (1990); and Jafari et al., Journal of

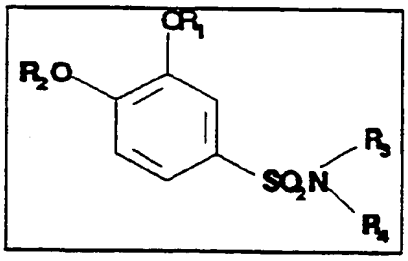
Infectious Diseases, 164:389-95, (1991). See also Wasan et al., Antimicrobial Agents and Chemotherapy, 35, (10):2046-48, (1991); and Luke et al., Journal of Infectious Diseases, 162:211-214, (1990)].

The ability to control the adverse effects of TNF is furthered by the use of the compounds which inhibit TNF in mammals who are in need of such use. There remains a need for compounds which are useful in treating TNF-mediated disease states which are exacerbated or caused by the excessive and/or unregulated production of TNF.

Summary of the invention

It has been found that novel compounds of formula (i) have ability to treat disease states, for example disease states associated with proteins that mediate cellular activity, for example by inhibiting tumour necrosis factor and/or by inhibiting phosphodiesterase IV. According to the invention, the novel compounds are of formula (i):

(i)



in which R_1 represents C_{1-6} alkyl (optionally substituted with one or more substituents chosen from amongst halogen, C_{1-6} alkoxy, aryloxy, arylalkyloxy, C_{1-6} alkylamino, arylalkylamino or arylamino) or cycloalkyl (optionally substituted with one or more substituents chosen from amongst halogen, C_{1-6} alkoxy, aryloxy, arylalkyloxy, C_{1-6} alkylamino, arylalkylamino or arylamino);

R_2 represents C1-3 alkyl optionally substituted with halogen;

R_3 represents H, arylalkyl, heteroarylalkyl, heterocycloalkyl, COR_7, $S(O)_mR_7$ or C_{1-6} alkyl optionally substituted with one or more substituents chosen from amongst hydroxy, C_{1-6} alkoxy, $-CO_2H$, CO_2R_8, $SO_2NR_9R_{10}$, $CONR_9R_{10}$, NR_5R_6, -CN, carbonyl oxygen, COR_7 or $S(O)_nR_7$;

when R_3 represents arylalkyl, heteroarylalkyl or heterocycloalkyl, the alkyl portion may be optionally substituted with one or more substituents chosen from amongst CO_2H, CO_2R_8 , $SO_2NR_9R_{10}$, $CONR_9R_{10}$, hydroxy, C_{1-6} alkoxy, NR_5R_6, COR_7, $S(O)_nR_7$, -CN or carbonyl oxygen and/or the aryl/heteroaryl/heterocyclo portion may be optionally substituted with one or more substituents C0-6 alkyl-R_{11} ;

R_4 represents a 5 or 6 membered saturated or unsaturated carbocyclic or heterocyclic ring to which ring is fused an aryl, heteroaryl, carbocyclic or heterocyclic ring, in which either or both rings may optionally be substituted by one or more substituents chosen from aryl, heterocyclo, heteroaryl, C_{1-6} alkyl (optionally substituted with aryl, heteroaryl, heterocyclo, carbonyl oxygen, hydroxy, NR_5R_6, C_{1-6} alkoxy, -CN, CO_2H, CO_2R_8 or $CONR_9R_{10}$), carbonyl oxygen, hydroxy, C_{1-6} alkoxy, -CN, CO_2H, CO_2R_8, $SO_2NR_9R_{10}$, $CONR_9R_{10}$, halogen, C_{1-6} alkoxy, hydroxy or $-NR_5R_6$;

R_5 and R_6, which may be the same or different, each represent H, aryl, heteroaryl, heterocyclo, C_{1-6} alkyl, arylalkyl, heteroarylalkyl, heterocycloalkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, arylsulphonyl, heteroarylsulphonyl, heterocyclosulphonyl, arylcarbonyl heteroarylcarbonyl, heterocyclocarbonyl or C_{1-6} alkylsulphonyl, provided that when R_5 is C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, arylsulphonyl, heteroarylsulphonyl, heterocyclosulphonyl, heteroarylcarbonyl,

heterocyclocarbonyl, arylcarbonyl or C_{1-6} alkylsulphonyl, R_6 is not C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, arylsulphonyl, heteroarylsulphonyl, heterocyclosulphonyl, heteroarylcarbonyl, heterocyclocarbonyl, arylcarbonyl or C_{1-6} alkylsulphonyl ;

R_7 represents aryl, heteroaryl, heterocyclo or C_{1-6} alkyl, any of which may be optionally substituted with one or more substituents chosen from amongst halogen, aryl, heteroaryl, heterocyclo, C_{1-6} alkoxy, hydroxy, CO_2H, CO_2R_8, $SO_2NR_9R_{10}$, $CONR_9R_{10}$, NR_5R_6 or carbonyl oxygen;

R_8 represents C_{1-6} alkyl, arylalkyl, heteroarylalkyl or heterocycloalkyl;

R_9 and R_{10}, which may be the same or different, each represent H, aryl, heteroaryl, heterocyclo, C_{1-6} alkyl, arylalkyl, heteroarylalkyl, heterocycloalkyl;

R_{11} represents H, aryl, heteroaryl, heterocyclo, hydroxy, C_{1-6} alkoxy, arylalkyloxy, heteroarylalkyloxy, heterocycloalkyloxy, $-CO_2H$, CO_2R_8, $SO_2NR_9R_{10}$, $CONR_9R_{10}$, halogen, -CN, $-NR_5R_6$, COR_7, $S(O)_nR_7$, -CN or carbonyl oxygen;

m represents 1-2; and

n represents 0-2;

and pharmaceutically acceptable salts thereof.

Description of the Invention

Preferred compounds of the invention include those in which, independently or in any combination:

R_1 is C_{1-6} alkyl (optionally substituted with aryloxy) or cycloalkyl;

R_2 is methyl optionally substituted with halogen;

R_3 is H, arylalkyl, heteroarylalkyl, SO_2R_7 or C_{1-6} alkyl (optionally substituted with one or more subdtituents chosen from hydroxy, $CONR_9R_{10}$, $SO_2NR_9R_{10}$, NR_5R_6, carbonyl oxygen, COR_7, SO_2R_7, CN, CO_2H or CO_2R_8);

R_4 is a 5 or 6 membered saturated ring (optionally substituted with C_{1-6} alkyl, carbonyl oxygen, hydroxy, CN, CO_2H, CO_2R_8) to which ring is fused an aryl or heteroaryl ring, optionally substituted with one or more substituents chosen from C_{1-6} alkyl, aryl, heteroaryl, hydroxy, C_{1-6} alkoxy, CO_2H, CO_2R_8, CN, $CONR_9R_{10}$, halogen or NR_5R_6;

R_5 and R_6, which may be the same or different, are H, C_{1-6} alkyl, arylalkyl, aryl, heteroarylalkyl, heteroaryl, C_{1-6} alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, arylsulphonyl, heteroarylsulphonyl or C_{1-6} alkylsulphonyl;

R_7 is C_{1-6} alkyl (optionally substituted with CN, CO_2H, CO_2R_8, $CONR_9R_{10}$, $SO_2NR_9R_{10}$, carbonyl oxygen or NR_5R_6), aryl or heteroaryl;

R_8 is C_{1-6} alkyl;

R_9 and R_{10}, which may be the same or different, are H, C_{1-6} alkyl, arylalkyl or heteroarylalkyl.

Suitable pharmaceutically acceptable salts are pharmaceutically acceptable base salts and pharmaceutically acceptable acid addition salts. Certain of the compounds of formula (i) which contain an acidic group form base salts. Suitable pharmaceutically acceptable base salts include metal salts, such as alkali metal salts for example sodium salts, or organic amine salts such as that provided with ethylenediamine.

Certain of the compounds of formula (i) which contain an amino group form acid addition salts. Suitable acid addition salts include pharmaceutically acceptable inorganic salts such as the sulphate, nitrate, phosphate, borate, hydrochloride and hydrobromide and pharmaceutically acceptable organic acid addition salts such as acetate, tartrate, maleate, citrate, succinate, benzoate, ascorbate, methane-sulphate, α-ketoglutarate, α-glycerophosphate and glucose-1-phosphate. The pharmaceutically acceptable salts of the compounds of formula (i) are prepared using conventional procedures.

It will be appreciated by those skilled in the art that some of the compounds of formula (i) may exist in more than one tautomeric form. This invention extends to all tautomeric forms. It will be appreciated that the compounds according to the invention can contain one or more asymmetrically substituted carbon atoms. The presence of one or more of these asymmetric centers in a compound of formula (i) can give rise to stereoisomers, and in each case the invention is to be understood to extend to all such stereoisomers, including enantiomers, and diastereoisomers and mixtures including racemic mixtures thereof.

When used herein the term alkyl whether used alone or when used as a part of another group includes straight and branched chain alkyl groups containing up to 6 atoms.. Alkyl-R_{11} means that the substituent R_{11} may be attached at any position of the alkyl group.Alkoxy means an alkyl-O- group in which the alkyl group is as previously described. Aryloxy means an aryl-O- group in which the aryl group is as defined below. Arylalkyloxy means an aryl-alkyl-O- group. Alkylamino means an alkyl-N- group in which the alkyl group is as previously defined, arylamino means aryl-N- and heteroarylamino means an heteroaryl-N- group (aryl and heteroaryl defined below). Cycloalkyl includes a non-

aromatic cyclic or multicyclic ring system of about 3 to 10 carbon atoms. The cyclic alkyl may optionally be partially unsaturated. Aryl indicates carbocyclic radicals containing about 6 to 10 carbon atoms. Arylalkyl means an aryl-alkyl- group wherein the aryl and alkyl are as described herein. Heteroarylalkyl means a heteroaryl-alkyl group and heterocycloalkyl means a heterocyclo-alkyl group. Alkyl amide includes both monoalkyl and dialkyl amides, in which the alkyl groups (previously descirbed) may be the same or different. Alkylcarbonyl means an alkyl-CO- group in which the alkyl group is as previously described. Arylcarbonyl means an aryl-CO- group in which the aryl group is as previously described. Arylsulphonyl means an aryl-SO_2- group in which the aryl group is as previously described. Heteroarylcarbonyl means a heteroaryl-CO- group and heterocyclocabonyl means a heterocyclo-CO- group. Heteroarylsulphonyl means a heteroaryl-SO_2- group and heterocyclosulphonyl means a heterocyclo-SO_2- group. Alkoxycarbonyl means an alkyloxy-CO- group in wich the alkoxy group is as previously desribed. Alkylsulphonyl means an alkyl-SO_2- group in which the alkyl group is as previously described. Carbonyl oxygen means a -CO- group. It will be appreciated that a carbonyl oxygen can not be a substituent on an aryl or heteroaryl ring. Carbocyclic ring means about a 5 to about a 10 membered monocyclic or multicyclic ring system which may saturated or partially unsaturated. Heterocyclic ring means about a 5 to about a 10 membered monocyclic or multicyclic ring system (which may saturated or partially unsaturated) wherein one or more of the atoms in the ring system is an element other than carbon chosen from amongst nitrogen, oxygen or sulphur atoms. Heteroaryl means about a 5 to about a 10 membered aromatic monocyclic or multicyclic hydrocarbon ring system in which one or more of the atoms in the ring system is an element other than carbon, chosen from amongst nitrogen, oxygen or sulphur. Heterocyclo means about a 5 to about a 10 membered saturated or partially saturated monocyclic or

multicyclic hydrocarbon ring system in which one or more of the atoms in the ring system is an element other than carbon, chosen from amongst nitrogen, oxygen or sulphur. Halogen means fluorine, chlorine, bromine or iodine.

"TNF mediated disease or disease states" means any and all disease states in which TNF plays a role, either by production of TNF itself, or by TNF causing another cytokine to be released, such as but not limited to IL-1 or IL-6. A disease state in which IL-1, for instance, is a major component, and whose production or action is exacerbated or secreted in response to TNF, would therefore be considered a disease state mediated by TNF. As TNF-β (also known as lymphotoxin) has close structural homology with TNF-α (also known as cachectin), and since each induces similar biologic responses and binds to the same cellular receptor, both TNF-α and TNF-β are inhibited by the compounds of the present invention and thus are herein referred to collectively as "TNF" unless specifically delineated otherwise.

This invention relates to a method for mediating or inhibiting the enzymatic activity or catalytic activity of PDE IV in a mammal in need thereof and for inhibiting the production of TNF in a mammal in need thereof, which comprises administering to said mammal an effective amount of a compound of Formula (i) or a pharmaceutically acceptable salt thereof.

PDE IV inhibitors are useful in the treatment of a variety of allergic and inflammatory diseases, including: asthma, chronic bronchitis, atopic dermatitis, atopic eczema, urticaria, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, inflammation of the eye, allergic responses in the eye, eosinophilic granuloma, psoriasis, Bechet's disease, erythematosis, anaphylactoid purpura nephritis, joint inflammation, arthritis, rheumatoid

arthritis and other arthritic conditions such as rheumatoid spondylitis and osteoarthritis, septic shock, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and brain, chronic glomerulonephritis, endotoxic shock and adult respiratory distress syndrome. In addition, PDE IV inhibitors are useful in the treatment of diabetes insipidus and conditions associated with cerebral metabolic inhibition, such as cerebral senility, senile dementia (Alzheimer's disease), memory impairment associated with Parkinson's disease, depression and multi-infarct dementia. PDE IV inhibitors are also useful in conditions ameliorated by neuroprotectant activity, such as cardiac arrest, stroke and intermittent claudication. Additionally, PDE IV inhibitors could have utility as gastroprotectants. A special embodiment of the therapeutic methods of the present invention is the treatment of asthma.

The viruses contemplated for treatment herein are those that produce TNF as a result of infection, or those which are sensitive to inhibition, such as by decreased replication, directly or indirectly, by the TNF inhibitors of Formula (i). Such viruses include, but are not limited to HIV-1, HIV-2 and HIV-3, cytomegalovirus (CMV), influenza, adenovirus and the Herpes group of viruses, such as, but not limited to, Herpes zoster and Herpes simplex.

This invention more specifically relates to a method of treating a mammal, afflicted with a human immunodeficiency virus (HIV), which comprises administering to such mammal an effective TNF inhibiting amount of a compound of Formula (i) or a pharmaceutically acceptable salt thereof.

The compounds of this invention may be also be used in association with the veterinary treatment of animals, other than humans, in need of inhibition of TNF production. TNF mediated diseases for treatment, therapeutically or

prophylactically, in animals include disease states such as those noted above, but in particular viral infections. Examples of such viruses include, but are not limited to feline immunodeficiency virus (FIV) or other retroviral infection such as equine infectious anaemia virus, caprine arthritis virus, visna virus, maedi virus and other lentiviruses.

The compounds of this invention are also useful in treating parasite, yeast and fungal infections, where such yeast and fungi are sensitive to upregulation by TNF or will elicit TNF production in vivo. A preferred disease state for treatment is fungal meningitis.

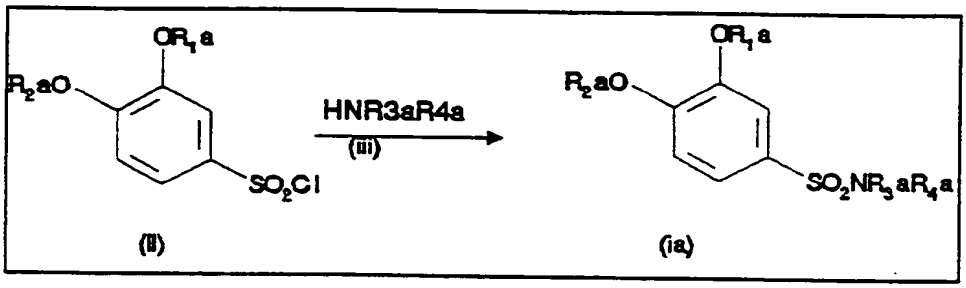
The compounds of formula (i) are preferably in pharmaceutically acceptable form. By pharmaceutically acceptable form is meant, inter alia, of a pharmaceutically acceptable level of purity excluding normal pharmaceutical additives such as diluents and carriers, and including no material considered toxic at normal dosage levels. A pharmaceutically acceptable level of purity will generally be at least 50% excluding normal pharmaceutical additives, preferably 75%, more preferably 90% and still more preferably 95%.

The invention further provides a process for the preparation of a compound of formula (i), in which R_1-R_{11} and m-n are as defined above. It will be appreciated that functional groups such as amino, hydroxyl or carboxyl groups present in the various compounds described below, and which it is desired to retain, may need to be in protected forms before any reaction is initiated. In such instances, removal of the protecting group may be the final step in a particular reaction. Suitable protecting groups for such functionality will be apparent to those skilled in the art. For specific details, see Protective Groups in Organic Synthesis, Wiley Interscience, TW Greene.

Thus the process for preparing compounds of formula (i) in which R_3 contains a $-CO_2H$ comprises deprotecting (for example by hydrolysis) a compound of formula (1) in which R_3 contains an appropriate $-CO_2R$ group wherein R represents a suitable protecting group (eg methyl).

It will be appreciated that where a particular stereoisomer of formula (i) is required, this may be obtained by conventional resolution techniques such as high performance liquid chromatography or the synthetic processes herein described may be performed using the appropriate homochiral starting material.

A process for the preparation of a compound of formula (ia) comprises reaction of an appropriate sulphonyl chloride of formula (ii) with a suitable amine of formula (iii)



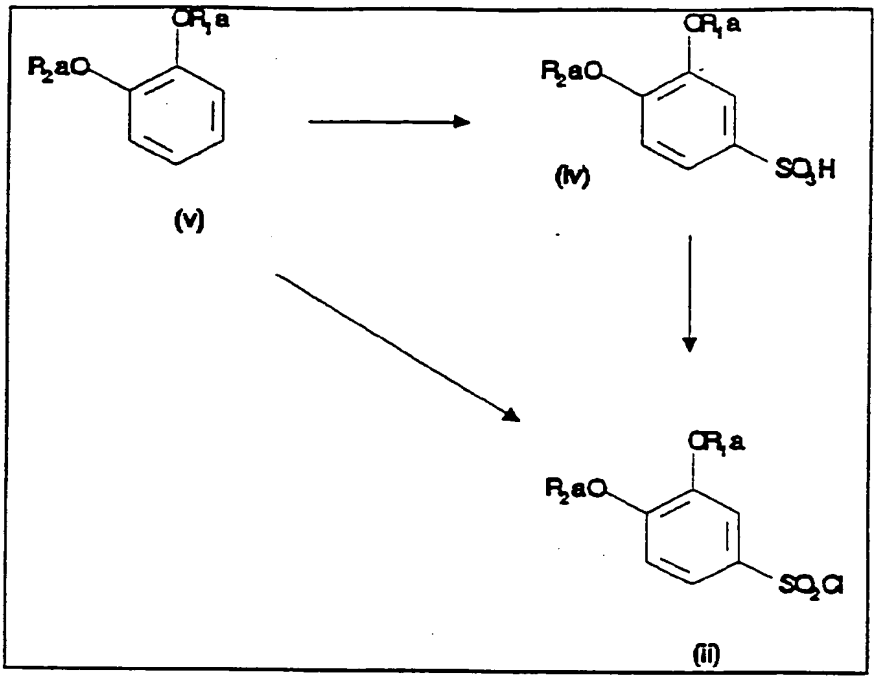
wherein R_{1a} represents R_1 as defined in relation to formula (i) or a group convertable to R_1 and R_{2a}-R_{4a} similarly represent R_2-R_4 or groups convertable to R_2-R_4 respectively; and thereafter, if required, converting any group R_{1a} to R_1 and/or R_{2a} to R_2 and/or R_{3a} to R_3 and/or R_{4a} to R_4.

The reaction of a sulphonyl chloride of formula (ii) with an amine of formula (iii) may be carried out under any suitable conditions known to those skilled in the art. Favourably the reaction is carried out in the presence of a suitable base, for example an amine such as

triethylamine, preferably in an appropriate solvent such as dichloromethane.

Sulphonyl chlorides of formula (ii) are either commercially available or are prepared using standard procedures known to those skilled in the art. For example a sulphonyl chloride of formula (ii) is conveniently prepared from the appropriate sulphonic acid (iv) by treatment with a suitable agent such as thionyl chloride or oxalyl chloride. An appropriate sulphonic acid may be prepared from a compound of formula (v) by sulphonylation using an appropriate sulphonylating agent, for example chlorosulphonic acid.Alternatively, a sulphonyl chloride of formula (ii) may be prepared directly from a compound of formula (v) by using excess chlorosulphonic acid. Compounds of formula (v) are either commercially available or may be prepared by standard procedures known to those skilled in the art.

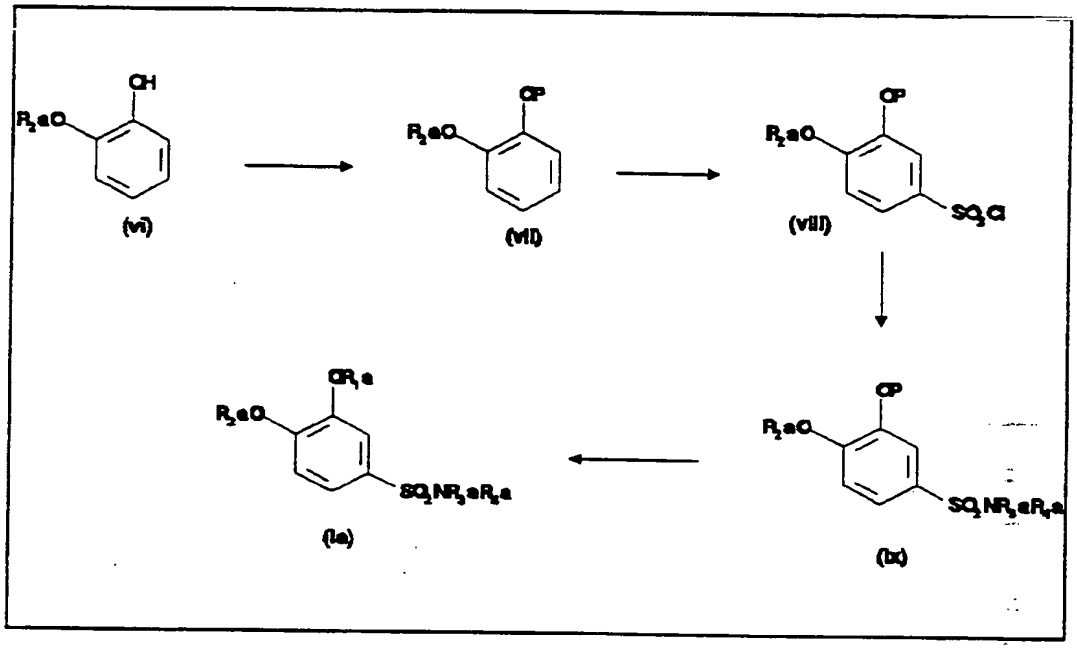
Alternatively, a sulphonyl chloride of formula (ii) may be prepared directly from a compound of formula (v) by using excess chlorosulphonic acid. Compounds of formula (v) are either commercially available or may be prepared by standard procedures known to those skilled in the art.



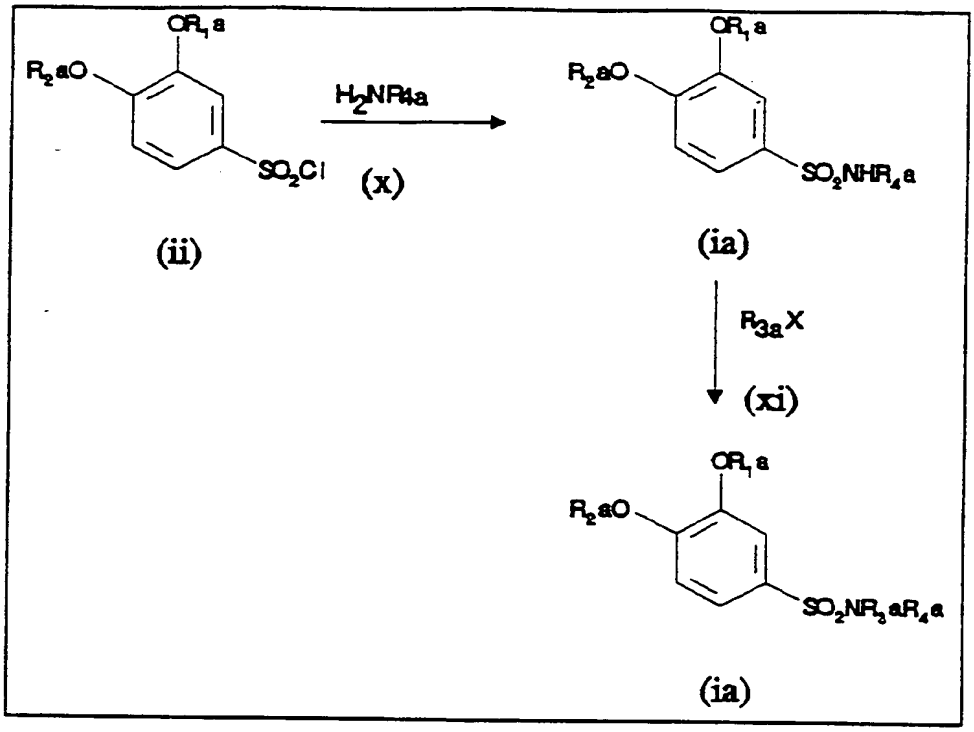
Amines of formula (iii) are either commercially available, previously described compounds or are prepared using standard procedures known to those skilled in the art. Some of the amines of formula (iii) are conveniently prepared by reductive amination of an appropriate carbonyl compound with a suitable amine. This amination may be carried out under any suitable standard conditions known to those skilled in the art.

An alternative method for the preparation of compounds of formula (ia) is shown below. This method involves the protection of an appropriate phenol of formula (vi) with a suitable protecting group (for example methanesulphonyl) under standard conditions known to those skilled in the art to provide a compound of formula (vii) and subsequent conversion to a sulphonyl chloride of formula (viii) by sulphonylation or chlorosulphonylation as descibed earlier. Reaction of sulphonyl chloride (viii) with an amine of formula (iii) as descibed earlier provides a compound of formula (ix). Deprotection under standard conditions known to those skilled in the art, followed by alkylation under

standard conditions known to those skilled in the art provides a compound of formula (ia).



A compound of formula (ia) may also be prepared by reaction of a sulphonyl chloride of formula (ii) with an amine of formula (x) to provide a compound of formula (ia) in which R_{3a} is H, followed by reaction with an appropriate agent of formula (xi).



wherein R_{1a}-R_{4a} are as defined earlier and X represents a suitable leaving group such as a halogen. The reaction of a sulphonyl chloride of formula (ii) with an amine of formula (x) may be carried out under any suitable conditions known to those skilled in the art. Favourably the reaction is carried out in the presence of a suitable base, for example an amine such as triethylamine, preferably in an appropriate solvent such as dichloromethane. Amines of formula (x) are either commercially available, previously described compounds or are prepared using standard procedures known to those skilled in the art. The reaction of a compound of formula (ia) in which R_3 is H with an agent of formula (xi) may be carried out under any suitable conditions known to those skilled in the art. Favourably the reaction is carried out using an appropriate base, such as sodium hydride, preferably in an appropriate solvent such as

dimethylformamide. Agents of formula (xi) are either commercially available, previously described compounds or are prepared using standard procedures known to those skilled in the art. Agent (xi) can be an alkylating agent such as propyl bromide, an acylating agent such as benzoyl chloride or a sulphonylating agent such as methanesulphonyl chloride.

A compound of formula (i) may also be prepared by interconversion of other compounds of formula (i). For example, a compound in which R_4 contains an alkoxy group may be prepared by appropriate alkylation of a compound in which R_4 contains a hydroxy group.

A compound of formula (i) or where appropriate a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, may be administered per se or, preferably, as a pharmaceutical composition also comprising a pharmaceutically acceptable carrier.

Accordingly, the present invention provides a pharmaceutical composition comprising a compound of formula (i) or where appropriate a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, and a pharmaceutically acceptable carrier.

The active compound may be formulated for administration by any suitable route, the preferred route depending upon the disorder for which treatment is required, and is preferably in unit dosage form or in a form that a human patient may administer to himself in a single dosage. Advantageously, the composition is suitable for oral, rectal, topical, parenteral administration or through the respiratory tract. Preparations may be designed to give slow release of the active ingredient.

The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion tecniques. In addition to the treatment of warm-blooded animals such as mice, rats, horses, cattle, sheep, dogs, cats, etc, the compounds of the invention are effective in the treatment of humans.

The compositions of the invention may be in the form of tablets, capsules, sachets, vials, powders, granules, lozenges, suppositories, reconstitutable powders, or liquid preparations such as oral or sterile parenteral solutions or suspensions. Topical formulations are also envisaged where appropriate.

In order to obtain consistency of administration it is preferred that a composition of the invention is in the form of a unit dose.

Unit dose presentation forms for oral administration may be tablets and capsules and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers for example microcrystalline cellulose, lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate; disintegrants, for example starch, polyvinylpyrrolidone, sodium starch glycollate or microcrystalline cellulose; or pharmaceutically acceptable wetting agents such as sodium lauryl sulphate.

The solid oral compositions may be prepared by conventional methods of blending, filling, tabletting or the like. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers.

Such operations are of course conventional in the art. The tablets may be coated according to methods well known in normal pharmaceutical practice, in particular with an enteric coating.

Oral liquid preparations may be in the form of, for example, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel, hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid; and if desired conventional flavouring or colouring agents.

Compositions may also suitably be presented for administration to the respiratory tract as a snuff or an aerosol or solution for a nebuliser, or as a microfine powder for insufflation, alone or in combination with an inert carrier such as lactose. In such a case the particles of active compound suitably have diameters of less than 50 microns, such as from 0.1 to 50 microns, preferably less than 10 microns, for example from 1 to 10 microns, 1 to 5 microns or from 2 to 5 microns. Where appropriate, small amounts of other anti-asthmatics and bronchodilators for example sympathomimetic amines such as isoprenaline, isoetharine, salbutamol, phenylephrine and ephedrine; corticosteroids such as prednisolone and adrenal stimulants such as ACTH may be included.

For parenteral administration, fluid unit dosage forms are prepared utilizing the compound and a sterile vehicle, and, depending on the concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions the compound can be dissolved in water for injection and filter sterilised before filling into a suitable vial or ampoule and sealing.

Advantageously, adjuvants such as local anaesthetic, a preservative and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilisation cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The compositions may contain from 0.1% to 99% by weight, preferably from 10-60% by weight, of the active material, depending on the method of administration.

Compounds of formula (i), or if appropriate a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, may also be administered as a topical formulation in combination with conventional topical excipients.

Topical formulations may be presented as, for instance, ointments, creams or lotions, impregnated dressings, gels, gel sticks, spray and aerosols, and may contain appropriate conventional additives such as preservatives, solvents to assist drug penetration and emollients in ointments and

creams. The formulations may contain compatible conventional carriers, such as cream or ointment bases and ethanol or oleyl alcohol for lotions.

Suitable cream, lotion, gel, stick, ointment, spray or aerosol formulations that may be used for compounds of formula (i) or if appropriate a pharmaceutically acceptable salt thereof, are conventional formulations well known in the art, for example, as described in standard text books such as Harry's Cosmeticology published by Leonard Hill Books, Remington's Pharmaceutical Sciences, and the British and US Pharmacopoeias.

Suitably, the compound of formula (i), or if appropriate a pharmaceutically acceptable salt thereof, will compromise from about 0.5 to 20% by weight of the formulation, favourably from about 1 to 10%, for example 2 to 5%.

The dose of the compound used in the treatment of the invention will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and the relative efficacy of the compound. However, as a general guide suitable unit doses may be 0.1 to 1000mg, such as 0.5 to 200, 0.5 to 100 or 0.5 to 10mg, for example 0.5, 1, 2, 3, 4 or 5mg; and such unit doses may be administered more than once a day, for example 2, 3, 4, 5 or 6 times a day, but preferably 1 or 2 times per day, so that the total daily dosage for a 70kg adult is in the range of about 0.1 to 1000mg, that is in the range of about 0.001 to 20 mg/kg/day, such as 0.007 to 3, 0.007 to 1.4, 0.007 to 0.14 or 0.01 to 0.5mg/kg/day, for example 0.01, 0.02, 0.04, 0.05, 0.06, 0.08, 0.1 or 0.2 mg/kg/day, and such therapy may extend for a number of weeks or months.

When used herein the term "pharmaceutically acceptable" encompasses materials suitable for both human and veterinary use.

The following illustrates the invention.

Intermediate 1 3-(1,2,3,4-Tetrahydronaphth-1-ylamino)propionitrile

Acrylonitrile (4.14g) was added dropwise with stirring at 55-65°C to 1,2,3,4-tetrahydro-1-naphthylamine (11.5g) over a period of 45 min. After addition the mixture was kept at 55-65°C for 12h then distilled under vacuum. Yield 6.8.g. Bp 163°/1.5mm

Intermediate 2 Ethyl-3-((N-indan-1-yl)amino)propanoate

Ethyl acrylate (2.1ml) was added dropwise to a solution of 1-aminoindane (1ml) in toluene (2.5ml). The mixture was stirred overnight at room temperature thenheated at reflux for 2 hours. The resultant mixture was evaporated in vacuo to afford a pale yellow oil. Yield 1.8g.
TLC R_f 0.5 (ethyl acetate)

Intermediate 3 5-Bromo-1-hydroximinoindane

5-Bromo-1-indanone (0.5g), hydroxylamine hydrochloride (0.4g) and sodium acetate (0.8g) were heated in ethanol (15ml) and water (5ml) to reflux for 2.5 hours then stirred at room temperatuure overnight. The reaction mixture was diluted with water (25ml) cooled to 0-5°C and the precipitate filtered off. Crystallisation from ethyl acetate and hexane afforded the title compound. Yield 0.43g.
TLC R_f 0.58 (15%ethyl acetate-dichloromethane)

Intermediate 4 5,6-Dimethoxy-1-hydroximinoindane

Prepared from 5,6-dimethoxyindanone by the above procedure. Yield 944mg.
TLC R_f 0.30 (50%ethyl acetate- hexane)

Intermediate 5 (±)-Methyl 3-hydroximino-indane-1-carboxylate

A solution of (±)-methyl indan-3-one-1-carboxylate (0.95g) in dry pyridine (15ml) was treated with hydroxylamine hydrochloride (0.7g) and heated at reflux for four hours under nitrogen. The solution was cooled and then poured onto ice (10ml). The product was extracted with ethyl acetate (2x50ml) and the extracts combined, washed with 2M aqueous hydrochloric acid (2x100ml), water (50ml), saturated aqueous sodium hydrogen carbonate (50ml), water (50ml) and saturated aqueous sodium chloride (50ml). The organic layer was dried over magnesium sulphate, filtered and the filtrate evaporated in vacuo to afford a yellow solid. Yield 1.09g.
Mp 125-130°C

Intermediate 6 (±)-Methyl 3-amino-indane-1-carboxylate

A mixture of (±)-methyl 3-hydroxyimino-indane-1-carboxylate (0.84g) and nickel chloride hexahydrate (1.95g) in dry methanol (50ml) under an atmosphere of nitrogen was cooled to -30°C and sodium borohydride (1.56g) added portionwise over 30 minutes. After 30 minutes the mixture was allowed to return to room temperature then partitioned between ethyl acetate (100ml) and dilute hydrochloric acid (400ml). The separated aqueous phase was basified to about pH10 using solid sodium hydroxide and extracted with ethyl acetate (2x100ml). These extracts were washed with water (50ml), saturated aqueous sodium chloride, dried over magnesium sulphate, filtered and evaporated in vacuo to afford a green oil . Yield 0.27g.

TLC R_f 0.1 (50%ethyl acetate-hexane)

Intermediate 7 5,6-Dimethoxy-1-aminoindane

Prepared from 5,6-dimethoxy-1-hydroximinoindane by the above procedure. Yield 415mg.
TLC R_f 0.20 (30% methanol- ethyl acetate)

Intermediate 8 (S)-3-Amino-2,5-dihydro-2-oxoquinoline

(S)-N-Boc-3-amino-2,5-dihydro-2-oxoquinoline (1.0g) was dissolved in dry dichloromethane (15ml) at room temperature and trifluoroacetic acid (4.5ml) added. After stirring for 48 hours dilute hydrochloric acid (2M, 50ml) was added and the phases separated. The organic phase was extracted with further acid (2x25ml). These combined aqueous phases were washed with dichloromethane (2x20ml), basified with dilute sodium hydroxide (2M) and extracted using ethyl acetate (3x50ml). The ethyl acetate extracts were washed with saturated brine (50ml), dried over magnesium sulphate and evaporated in vacuo to give the title amine. Yield 152mg.
TLC R_f 0.18 (ethyl acetate)

Intermediate 9 (S)-N-Boc-3-amino-2,5-dihydro-2-oxoquinoline

Di-tert-butyl dicarbonate (34.9g) in methanol (50ml) was added dropwise to a solution of (S)-N-acetyl-3-(2-nitrophenyl)alanine (28g) in methanol (90ml) and water (140ml) at pH10. Autoaddition of aqueous sodium hydroxide (5M, 50ml) overnight maintained the stirred mixture at pH10. The solution was concentrated in vacuo to remove the methanol and then adjusted to pH3 using aqueous potassium hydrogen sulphate (1M). Ethyl acetate (3x400ml) extracts of this mixture were dried over magnesium sulphate, filtered and evaporated in vacuo to yield a cream solid (14g), (S)-N-Boc-3-(2-nitrophenyl)alanine. This product (8.9g) was

hydrogenated in 90% ethanol (90ml) with platinum oxide (450mg) catalysis. The isolated crude material (8.2g) was chromatographed using 50%ethyl acetate in heptane then rechromatographed with the same solvent system to afford a white solid. Yield 3.5g.

TLC R_f 0.5 (50%ethyl acetate in heptane)

mp 67°C (dec)

Intermediate 10 (S)-N-Acetyl-3-(2-nitrophenyl)alanine

Methanol (500ml) and sodium methoxide (25g) were heated to 50°C and diethyl acetamidomalonate (100g) was added. The heat was removed and 2-nitrobenzylbromide (100g) introduced slowly over 15 minutes so as to maintain the temperature about 50°C. After 20minutes water (500ml) was added, the mixture concentrated in vacuo to a volume of about 500ml then cooled in ice to give a precipitate. This was collected by filtration and dried in vacuo to afford an off-white solid (140g) of (±)-methyl-N-acetyl-2-carboethoxy-3-(2-nitrophenyl)alanine.

Hydrolysis of the diester (121g) was achieved by heating to reflux in methanol (100ml) and hydrochloric acid (6N, 500ml) for 20 hours. The cooled mixture was concentrated to give a brown solid. Water (300ml) was added followed by sodium hydroxide solution with cooling to attain pH6.5. This solution was concentrated to half volume and acetone (300ml) added to produce a precipitate which was collected by filtration and then dried in vacuo to yield a buff solid (77.5g), 3-(2-nitrophenyl)alanine.

Acetylation of 3-(2-nitrophenyl)alanine (77g) with acetic anhydride (69.3ml) in acetic acid (800ml) was achieved by stirring at room temperature overnight. The solid was collected by filtration and washed with diethyl ether to afford an off-white product (74g).

Resolution of the (±)-N-acetyl-3-(2-nitrophenyl)alanine (74g) was effected by stirring with Amano Acylase 30,000 (7.4g) in aqueous potassium dihydrogen phosphate

(10mM,1110ml) at 40°C for 24 hours. The mixture was adjusted to pH 6.5- 7 and concentrated in vacuo to about 200ml then acetone (200ml) added to give a precipitate. This was filtered off, washed with acetone and dried in vacuo to afford an off-white solid, (S)-N-acetyl-3-(2-nitrophenyl)alanine. Yield 34g.
mp 197.5 - 198°C (dec)
98%ee by Chirex PEN using 90% 2mM $CuSO_4$ / 10% methanol at 254nm.

Intermediate 11 (±)-Methyl indan-3-one-1-carboxylate

Acetyl chloride (3ml) was carefully added to methanol (60ml) at room temperature. The solution was treated with (±)-3-oxo-1- indane carboxylic acid (10g) and the mixture heated at 60°C for two hours. The reaction was cooled and the solvent removed in vacuo. The residue was dissolved in ethyl acetate (100ml) and washed with saturated aqueous sodium hydrogen carbonate (50ml), water (50ml) and saturated aqueous sodium chloride (50ml). The organic layer was then dried over magnesium sulphate, filtered and the filtrate evaporated in vacuo to yield a colourless solid Yield 10g.
Mp 44.0-45.5°C

Intermediate 12 (cis)-7-Ketobenzo[d]-6-azabicyclo[3.2.0]heptane

A solution of indene (5.0ml) in diethyl ether (11ml) was treated with a solution of chlorosulphonylisocyanate (5.5ml) in diethyl ether (11ml) at room temperature. After observing a mild exotherm the solution was stirred at room temperature for 90 minutes. Hexane (32ml) was added and the reaction cooled to 0°C. Collection of the precipitate afforded the desired sulphonyl chloride as an off-white solid (9.0g). This solid (9g)was added to a solution of benzenethiol (8ml) in acetone (45ml) at -25°C. A solution

of pyridine (4ml) in acetone (18ml) was added dropwise over a 30 minute period and the solution stirred for a further 90 minutes at -25°C before adding water (45ml). The precipitate was removed by filtration and the filtrate extracted with diethyl ether (2x75ml). The extracts were combined, dried over sodium sulphate, filtered and the filtrate evaporated in vacuo. Recrystallisation from ethyl acetate -hexane afforded an off white solid. Yield 1.3g. m.p 138-140°C

Intermediate 13 (cis)-6-t-Butyloxycarbonyl-7-ketobenzo[d]-6-azabicyclo-[3.2.0]heptane

A solution of 7-ketobenzo[d]-6-azabicyclo[3.2.0]heptane (281mg) in dichloromethane (10ml) was treated with triethylamine (270ml) and dimethylaminopyridine (2mg) at 0°C under nitrogen. Di-t-butyl dicarbonate (450ml) was added dropwise to the solution and the mixture stirred at 0°C for 20 minutes. After warming to room temperature the reaction was stirred for a further three hours before evaporating the solvent in vacuo. Purification by column chromatography eluting with 40% ethyl acetate- hexane afforded a colourless oil . Yield 440mg.
TLC R_f 0.60 (50%ethyl acetate- hexane)

Intermediate 14 (cis)-Methyl 2-t-butyloxycarbonyl-aminoindane-1-carboxylate

(cis)-6-t-Butyloxycarbonyl-7-ketobenzo[d]-6-azabicyclo[3.2.0]heptane (98mg) was treated with a 2M solution of ammonia in methanol (5ml). The reaction was stirred at room temperature for 15 minutes and then the solvent was evaporated in vacuo. Recrystallisation from ethyl acetate-hexane afforded (cis)- 2-t-butyloxycarbonylamino-1-indane carboxamide. Subsequent recrystallisation of the mother liquors afforded the desired methyl ester as a white solid. Yield 15mg.

TLC R_f 0.50 (30%ethyl acetate- hexane)

Intermediate 15 (cis/trans)-Methyl 2-t-butyloxycarbonyl-aminoindane-1-carboxylate

A solution of (cis)-6-t-butyloxycarbonyl-7-ketobenzo[d]-6-azabicyclo[3.2.0]heptane (440mg) in anhydrous methanol (20ml) was treated with a catalytic ammount of sodium methoxide . The rection was stirred at room temperature for 10 minutes and then the solvent was evaporated in vacuo. The residue was partitioned between water (20ml) and dichloromethane (20ml). The aqueous phase was separated, made acidic with saturated aqueous ammonium chloride and re-extracted with dichloromethane (20ml). The extracts were combined, dried over magnesium sulphate and filtered. The filtrate was evaporated in vacuo to afford an off white solid. Yield 485mg.

TLC R_f 0.50 (30%ethyl acetate- hexane)

^1H NMR showed that the chiral centre of the ester had been racemised.

Intermediate 16 (±)-1-Azido-2-hydroxyindane

3-Chloroperoxybenzoic acid (50-60%, 15g) was added portionwise over 10 minutes to a stirred solution of indene (5g) in sodium hydrogen carbonate solution (0.3 M, 400ml) and dichloromethane (400ml) at 0°C. The mixture was stirred vigorously at room temperature for 5 hours followed by a further addition of 3-chloroperoxybenzoic acid (15g) at 0°C over a 10 minute period and the reaction was stirred at room temperature overnight. The reaction mixture was separated and the aqueous phase further extracted with dichloromethane (2x 100ml). The combined organic phases were washed with cold 1M sodium hydroxide solution until no peroxide was detected by Merck™ Quent papers. The organics were dried over magnesium sulphate, filtered and concentrated in vacuo to yield crude indan-1,2-oxide as a

pale yellow oil. Yield 4.7g. Sodium azide (3.94g) in water (50ml) was added dropwise over a 30 minute period to a stirred solution of indan-1,2-oxide (4g) in 1,4-dioxane (50ml). After stirring at room temperature overnight the reaction was extracted with diethyl ether (3x50ml). The combined organics were dried over magnesium sulphate, filtered and cautiously concentrated in vacuo to afford the title compound as an orange oil. Yield 3.48g.
TLC R_f 0.37 (30% ethyl acetate in hexane)

Intermediate 17 (±)-1-Amino-2-hydroxyindane

A mixture of (±)-1-azido-2-hydroxyindane (0.5g) and triphenylphosphine (0.79g) in water (0.5ml) and tetrahydrofuran (20ml) was stirred at room temperature overnight. The reaction mixture was concentrated in vacuo and purified by column chromatography eluting with 5% methanol/ 1% triethylamine in dichloromethane providing the title compound as a beige solid. Yield 0.39g.
TLC R_f 0.20 (5% methanol in dichloromethane)

Example 1 N-(Indan-1-yl)-3,4-dimethoxybenzenesulphonamide

1-Aminoindane (5.04g) was dissolved in dichloromethane (100ml) and triethylamine (4.22g) added followed by 3,4-dimethoxybenzenesulphonyl chloride (8.99g). The mixture was stirred at room temperature for 4h then washed (2x100ml) with water. The organic layer was dried and evaporated to give a solid which was recrystallised from ethanol. Yield 10.83g.
TLC R_f 0.46 (50% ethyl acetate in hexane)
mp 138-140°

The following compounds were prepared using the above procedure.

Example 2 (R)-N-(Indan-1-yl)-3,4-dimethoxybenzenesulphonamide

Prepared from (R)-1-aminoindane.
Trituration with diethyl ether afforded a buff coloured solid. Yield 237mg.
TLC R_f 0.45 (40% ethyl acetate in hexane)
mp 119-120°C

Example 3 (S)-N-(Indan-1-yl)-3,4-dimethoxybenzenesulphonamide

Prepared from (S)-1-aminoindane.
Trituration with diethyl ether afforded a buff coloured solid. Yield 249mg.
TLC R_f 0.45 (40% ethyl acetate in hexane)
mp 130-131°C

Example 4 3,4-Dihydro-3S-(3,4-dimethoxybenzenesulphonamido)-2(1H)-quinolinone

Prepared from 3S-amino-3,4-dihydro-2(1H)-quinolinone.
Isolated as a colourless powder not requiring any purification. Yield 83mg.
TLC R_f 0.15 (50% ethyl acetate in hexane)
mp 228 - 229°C

Example 5 (±)-Methyl 3-(3,4-dimethoxybenzene-sulphonamido) indane-1-carboxylate

Prepared from (±)-methyl 3-amino-indane-1-carboxylate.
Purification by column chromatography eluting with 10% -60% ethyl acetate-hexane followed by recrystallisation from ethyl acetate -hexane afforded a colourless solid.Yield 120mg.
TLC R_f 0.44 (50% ethyl acetate in hexane)

mp 160-162°C

Example 6 Ethyl 3-((N-indan-1-yl)-3,4-dimethoxybenzenesulphonamido)propionate

Prepared from ethyl 3-((N-indan-1-yl)amino)propionate. Purification by column chromatography eluting with 50% ethyl acetate in hexane then crystallisation from ethyl acetate- hexane afforded colourless crystals. Yield 630mg.
TLC R_f 0.40 (50% ethyl acetate in hexane)
mp 110.5 - 111°C

Example 7 N-(5,6-Dimethoxyindan-1-yl)-3,4-dimethoxybenzenesulphonamide

Prepared from 5,6-dimethoxy-1-aminoindane.
Purification by recrystallisation from ethyl acetate - hexane afforded a colourless solid. Yield 672mg.
TLC R_f 0.20 (50% ethyl acetate in hexane)
mp 149-150°C

Example 8 N-(1,2,3,4-tetrahydronapth-1-yl)-3,4-dimethoxybenzene-sulphonamide

Prepared from 1,2,3,4-tetrahydro-1-napthylamine. The product was recrystallised from acetonitrile.
TLC R_f 0.58 (50% ethyl acetate in hexane)
mp 184-187°

Example 9 (±)-N-(2-Hydroxyindan-1-yl)-3,4-dimethoxybenzenesulphonamide

Prepared from (±)-1-amino-2-hydroxyindane.
Recrystallisation from ethyl acetate-hexane afforded the title compound as a beige solid.
Yield 0.25g.
TLC R_f 0.12 (50% ethyl acetate in hexane)

mp 147.5-148.5°C

Example 10 N-Cyanoethyl-N-(indan-1-yl)-3,4-dimethoxybenzenesulphonamide

A mixture of 1-aminoindane (4.87g) and acrylonitrile (1.94g) was heated at 60° for 11h. The resulting mixture was distilled under vacuum to remove any unreacted 1-aminoindane and the residue was used in the next step without further purification.

The preceding oil (3.22g) was dissolved in dichloromethane (75ml) and triethylamine (1.72g) was added followed by 3,4-dimethoxybenzenesulphonyl chloride (4.02g). The mixture was washed with water (2x75ml) and then dried and evaporated to give a solid which was recrystallised from toluene. Yield 3.66g.
TLC R_f 0.46 (50% ethyl acetate in hexane)
mp 159-162°

Example 11 N-Cyanoethyl-N-(1,2,3,4tetrahydronaphth-1-yl)-3,4-dimethoxy benzenesulphonamide

3-(1,2,3,4-Tetrahydronaphth-1-ylamino)propionitrile was dissolved in dichloromethane (100ml) and triethylamine (2.53g) added. To this stirred mixture was added 3,4-dimethoxybenzenesulphonyl chloride (5.21g) and the mixture stirred at room temperature overnight. It was washed (2x 100ml) with water then with 2M hydrochloric acid followed by 10% sodium hydroxide solution. Evaporation of the dried organic layer gave an oil which was subjected to column chromatography on silica using initially dichloromethane then ethyl acetate as eluent. The resulting product was recrystallised from ethanol. Yield 1.36g.
TLC R_f 0.46 (50% ethyl acetate in hexane)
mp 131-133°

Example 12 N-[1,2,3,4-Tetrahydro-6acetamidonaphth-1-yl]-3,4-dimethoxybenzenesulphonamide

A solution of 6-acetamido-1-tetralone (0.71g), ammonium acetate (2.7g), and sodium cyanoborohydride (0.15g) in methanol (10ml) was stirred at room temperature under nitrogen for 66 hours. The solution was acidified with concentrated hydrochloric acid to pH 2 and concentrated in vacuo to remove the methanol. The residue was suspended in water (100ml) and extracted with ethyl acetate (2x75ml). The aqueous phase was made alkaline (pH 10) with solid potassium hydroxide and extracted with ethyl acetate (2x75ml). The latter extracts were combined, dried over magnesium sulphate, filtered and the filtrate evaporated in vacuo to yield a pale yellow oil (0.5g)

A solution of 3,4-dimethoxybenzenesulphonyl chloride (0.24g) in anhydrous tetrahydrofuran (2ml) was added to a cooled solution of the 6-acetamido-1-amino-1,2,3,4-tetrahydronaphthalene (0.21g) and triethylamine (156ml) in tetrahydrofuran (5ml). The reaction was stirred at 0^0C for 10 minutes and then allowed to warm to room temperature. After 17 hours the solution was concentrated in vacuo and the residue partitioned between water (40ml) and ethyl acetate (40ml). The aqueous layer was re-extracted with ethyl acetate (40ml) and the organic extracts combined. The solution was dried over magnesium sulphate, filtered and the filtrate evaporated in vacuo.

Purification by column chromatography eluting with 10% methanol/ 45% ethyl acetate/ 45% hexane provided the title compound as a pale yellow foam. Yield 0.28g.

TLC R_f 0.35 (10%methanol/ 45% ethyl acetate/ 45% hexane)

FTIR (KBr) 3436, 3383, 2938, 1689, 1590, 1509, 1407, 1330, 1262, 1153, 1096, 1022 cm^{-1}

The following compounds were prepared using the above procedure from the appropriate starting materials.

Example 13 N-[5-Acetamidoindan-1-yl]-3,4-dimethoxybenzenesulphonamide

Yield 0.05g
TLC R_f 0.23 (10% methanol/ 45% ethyl acetate/ 45% hexane)
FTIR (KBr) 3437, 3378, 2969, 1689, 1592, 1509, 1423, 1408, 1332, 1262, 1237, 1156, 1140, 1096, 1023 cm^{-1}

Example 14 N-[5-Chloroindan-1-yl]-3,4-dimethoxybenzenesulphonamide

Purification by column chromatography eluting with 50% ethyl acetate in hexane provided the title compound which was recrystallised from ethyl acetate/hexane to yield off-white coloured needles. Yield 0.17g.
TLC R_f 0.38 (50% ethyl acetate in hexane)
mp 140-141°

Example 15 N-[5-Methoxyindan-1-yl]-3,4-dimethoxybenzenesulphonamide

Purification by column chromatography eluting with 50% ethyl acetate in hexane provided the title compound which was recrystallised from ethyl acetate/hexane to yield light-brown needles. Yield 0.07g.
TLC R_f 0.33 (50% ethyl acetate in hexane)
mp 152-153°

Example 16 N-Indan-2-yl-3,4-dimethoxybenzenesulphonamide

Purification by column chromatography eluting with 55% ethyl acetate in hexane then crystallisation from ethyl acetate- hexane afforded a beige solid. Yield 52.5mg.
TLC R_f 0.60 (60% ethyl acetate in hexane)
mp 127.0 - 127.5°C

Example 17 N-(4-Methoxyindan-1-yl)-3,4-dimethoxybenzenesulphonamide

Purification by column chromatography eluting with 50% ethyl acetate in hexane then crystallisation from ethyl acetate- hexane afforded a colourless crystalline solid. Yield 195mg.
TLC R_f 0.35 (50% ethyl acetate in hexane)
mp 142.5 - 143.0°C

Example 18 N-(6-Methoxyindan-1-yl)-3,4-dimethoxybenzenesulphonamide

Purification by column chromatography eluting with 50% ethyl acetate in hexane afforded a colourless crystalline solid. Yield 233mg.
TLC R_f 0.37 (50% ethyl acetate in hexane)
mp 142 - 143°C

Example 19 N-(5-bromoindan-1-yl)-3,4-dimethoxybenzenesulphonamide

A mixture of 5-bromo-1-hydroximinoindane (0.15g) and nickel chloride hexahydrate (315mg) in dry methanol (5ml) under an atmosphere of nitrogen was cooled to -30°C and sodium borohydride (0.25g) added portionwise over 30 minutes. After 30 minutes the mixture was allowed to return to room temperature then partitioned between ethyl acetate (40ml) and dilute hydrochloric acid (80ml). The separated aqueous phase was basified to about pH10 using pellets of potassium hydroxide and extracted with ethyl acetate (2x40ml). These extracts were dried over magnesium sulphate, filtered and evaporated in vacuo to afford a brown oil (0.11g) of 1-amino-5-bromoindane. This crude amine was used directly following the general procedure for the preparation of sulphonamides using triethylamine in dichloromethane.

Purification by column chromatography eluting with 15% ethyl acetate in dichloromethane then crystallisation from ethyl acetate- hexane afforded a colourless solid. Yield 0.04g.

TLC R_f 0.59 (15% ethyl acetate in dichloromethane)
mp 132.5 - 133.5°C

Example 20 (cis)(±)-Methyl 1-(3,4-dimethoxybenzenesulphonamido)indane-2-carboxylate

A solution of (cis)- methyl 2-t-butyloxycarbonylaminoindane-1-carboxylate (20mg) in anhydrous dichloromethane (1.25ml) at 0°C under nitrogen was treated dropwise with trifluoroacetic acid (0.25ml). The reaction was allowed to warm to room temperature and stirred for 35 minutes. The solvent was removed in vacuo and re-evaporated from toluene (5ml) to afford a clear oil. The oil was dissolved in dichloromethane (0.5ml) and treated with triethylamine (40ml). The solution was cooled to 0°C and treated dropwise with a solution of 3,4-dimethoxysulphonyl chloride (16mg) in dichloromethane. The reaction was stirred at 0°C for 30 minutes and then at room temperature for six hours. Dichloromethane (4ml) was then added and the organic solution washed with saturated ammonium chloride (5ml). The organic layer was dried over magnesium sulphate, filtered and the filtrate evaporated in vacuo. Purification by column chromatography eluting with 50% ethyl acetate-hexane followed by recrystallisation from ethyl acetate -hexane afforded a colourless solid. Yield 10mg.

TLC R_f 0.30 (50% ethyl acetate in hexane)
mp 123-124°C

Example 21 (trans)(±)-Methyl 1-(3,4-dimethoxybenzenesulphonamido)-indane-2-carboxylate

Prepared from (cis/trans)- methyl 2-t-butyloxycarbonylaminoindane-1-carboxylate by the above procedure.

Purification by column chromatography eluting with 50% ethyl acetate-hexane afforded the cis (20mg) and trans (18mg) products. Recrystallisation from ethyl acetate - hexane afforded the trans isomer as a sticky colourless solid.

TLC R_f 0.30 (50% ethyl acetate in hexane)

Example 22 N-Indan-1-yl-N-(4-pyridylmethyl)-3,4-dimethoxybenzene-sulphonamide

A solution of 3,4-dimethoxy-N-indan-1-ylbenzenesulphonamide (0.35g) in dry N,N-dimethylformamide (3ml) was cooled to 0-5°C and sodium hydride (84mg) added. 4-Chloromethylpyridine hydrochloride (175mg) was added, the cooling bath removed after 30 minutes and the mixture stirred at room temperature overnight. The reaction mixture was evaporated in vacuo and the product extracted into ethyl acetate (2x25ml) from the residue obtained in water (25ml).

Purification by column chromatography eluting with ethyl acetate afforded a colourless oil. Yield 340mg.

TLC R_f 0.40 (ethyl acetate)

FTIR (film) νmax ; 3606, 3370, 2937, 1600, 1588, 1508 cm^{-1}

The following examples were prepared using the above procedure.

Example 23 N-Indan-1-yl-N-(3-pyridylmethyl)-3,4-dimethoxybenzene-sulphonamide

Prepared from 3-chloromethylpyridine hydrochloride.

Purification by column chromatography eluting with ethyl acetate then crystallisation from ethyl acetate- hexane afforded colourless crystals.Yield 277mg.
TLC R_f 0.40 (ethyl acetate)
mp 115 - 116°C

Example 24 N-Indan-1-yl-N-(2-pyridylmethyl)-3,4-dimethoxybenzene-sulphonamide

As above using 2-chloromethylpyridine hydrochloride. Purification by column chromatography eluting with 66% ethyl acetate in hexane afforded an off-white powder.Yield 451mg.
TLC R_f 0.30 (50% ethyl acetate in hexane)
mp 142.5 - 143°C

Example 25 N-(Indan-1-yl)-N-[4-(2-methylthiazolylmethyl)]-3,4-dimethoxy-benzenesulphonamide

Purification by column chromatography eluting with 15% ethyl acetate-dichloromethane afforded a colourless oil.Yield 192mg.
TLC R_f 0.25 (50% ethyl acetate in hexane)
FTIR (KBr) 2936, 1508, 1331, 1262, 1237, 1138, 1094, 1021cm^{-1}

Example 26 N-(Indan-1-yl)-N-(methanesulphonyl)-3,4-dimethoxybenzene-sulphonamide

Purification by column chromatography eluting with 40% ethyl acetate-hexane followed by recrystallisation from diethyl ether -hexane afforded a colourless solid.Yield 65mg.
TLC R_f 0.47 (50% ethyl acetate in hexane)
mp 109-110°C

Example 27 3-[(N-Indan-1-yl)-3,4-dimethoxybenzenesulphonamido]-propanoic acid

A solution of ethyl-3-((N-indan-1-yl)-3,4-dimethoxybenzenesulphonamido)propanoate (250mg) in ethanol (6ml) was treated with an aqueous solution of sodium hydroxide (2M, 6ml) and the reaction mixture stirred at room temperature overnight. The reaction mixture was acidified with glacial acetic acid (12ml) and the solvent evaporated in vacuo. The residue was partioned between ethyl acetate (30ml) and water (30ml) and the aqueous layer acidified further with concentrated hydrochloric acid before extracting with ethyl acetate (2x25ml). The organic extracts were combined, washed with water (50ml), dried over magnesium sulphate, filtered and the filtrate evaporated in vacuo. The residue was recrystallised from diethyl ether -hexane to afford a colourless foam. Yield 233mg.

TLC R_f 0.30 (1%AcOH/ 50% ethyl acetate/ hexane)

FTIR (KBr) 2938, 1712, 1509, 1331, 1262, 1237, 1138, 1095 and 1020cm^{-1}

Example 28 N-(Pyrindan-7-yl)-3,4-dimethoxybenzenesulphonamide

Sodium cyanoborohydride (210mg) was added to a suspension of ammonium acetate (2.6g) and 5,6-dihydro-7H- pyrinden-7-one (450mg) [Chem. Ber., 1991, 124, 571-6] in methanol (11ml), and the resulting mixture stirred for 3 days at room temperature. The reaction mixture was acidified to pH2 with 6N hydrochloric acid and the methanol was evaporated in vacuo. The residue was partitioned between ethyl acetate (50ml) and water (60ml). The aqueous phase was reextracted with ethyl acetate (50ml), then basified with solid potassium hydroxide pellets to pH12. The aqueous phase was then extracted into ethyl acetate (3 x 75ml) with the addition of sodium chloride. The combined organic phases were dried (magnesium sulphate), filtered

and evaporated to afford crude 7-aminopyrindane as a brown oil. A solution of the crude amine and triethylamine (330ml) in dichloromethane was cooled to 0°C and a solution of 3,4-dimethoxybenzenesulphonamide (511mg) in dichloromethane (3ml) was added dropwise over 15 minutes. The reaction mixture was stirred at 0°C for 15 minutes, then at room temperature for 25h. The reaction mixture was diluted with dichloromethane (25ml), washed with dilute aqueous sodium hydrogen carbonate solution (25ml), dried (magnesium sulphate), filtered and evaporated in vacuo. Purification by flash chromatography (silica, 70g, eluting with ethyl acetate) furnished the title compound (95mg) as a pale pink foam.

TLC R_f 0.33 (ethyl acetate)
FTIR 3276, 2938, 1589, 1509, 1331, 1263, 1156, 1139, 1094, 1021, 914, 732, 581cm^{-1}

Assay methods

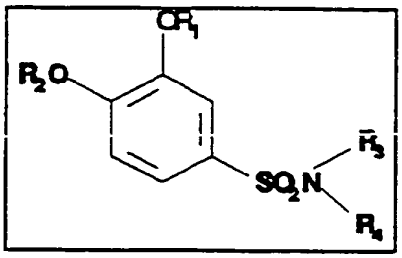
The assays used to confirm the phosphodiesterase IV inhibitory activity of compounds of formula (i) are standard assay procedures as disclosed by Schilling et al Anal. Biochem. 216 154 (1994), Thompson and Strada Adv. Cycl. Nucl. Res. 8 119 (1979) and Gristwood and Owen Br. J. Pharmacol. 87 91P (1986).

Compounds of formula (i) have exhibited activity at levels consistent with those believed to be useful in treating phosphodiesterase IV related disease states in those assays.

CLAIMS

1. Compounds of the general formula (i)

(i)



in which R_1 represents C_{1-6} alkyl (optionally substituted with one or more substituents chosen from amongst halogen, C_{1-6} alkoxy, aryloxy, arylalkyloxy, C_{1-6} alkylamino, arylalkylamino or arylamino) or cycloalkyl (optionally substituted with one or more substituents chosen from amongst halogen, C_{1-6} alkoxy, aryloxy, arylalkyloxy, C_{1-6} alkylamino, arylalkylamino or arylamino);

R_2 represents C1-3 alkyl optionally substituted with halogen;

R_3 represents H, arylalkyl, heteroarylalkyl, heterocycloalkyl, COR_7, $S(O)_mR_7$ or C_{1-6} alkyl optionally substituted with one or more substituents chosen from amongst hydroxy, C_{1-6} alkoxy, $-CO_2H$, CO_2R_8, $SO_2NR_9R_{10}$, $CONR_9R_{10}$, NR_5R_6, -CN, carbonyl oxygen, COR_7 or $S(O)_nR_7$;

when R_3 represents arylalkyl, heteroarylalkyl or heterocycloalkyl, the alkyl portion may be optionally substituted with one or more substituents chosen from amongst CO_2H, CO_2R_8, $SO_2NR_9R_{10}$, $CONR_9R_{10}$, hydroxy, C_{1-6} alkoxy, NR_5R_6, COR_7, $S(O)_nR_7$, -CN or carbonyl oxygen and/or the aryl/heteroaryl/heterocyclo portion may be optionally substituted with one or more substituents C0-6 alkyl-R_{11} ;

R_4 represents a 5 or 6 membered saturated or unsaturated carbocyclic or heterocyclic ring to which ring is fused an aryl, heteroaryl, carbocyclic or heterocyclic ring,
in which either or both rings may optionally be substituted by one or more substituents chosen from aryl, heterocyclo, heteroaryl, C_{1-6} alkyl (optionally substituted with aryl, heteroaryl, heterocyclo, carbonyl oxygen, hydroxy, NR_5R_6, C_{1-6} alkoxy, -CN, CO_2H, CO_2R_8 or $CONR_9R_{10}$), carbonyl oxygen, hydroxy, C_{1-6} alkoxy, -CN, CO_2H, CO_2R_8, $SO_2NR_9R_{10}$, $CONR_9R_{10}$, halogen, C_{1-6} alkoxy, hydroxy or $-NR_5R_6$;

R_5 and R_6, which may be the same or different, each represent H, aryl, heteroaryl, heterocyclo, C_{1-6} alkyl, arylalkyl, heteroarylalkyl, heterocycloalkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, arylsulphonyl, heteroarylsulphonyl, heterocyclosulphonyl, arylcarbonyl heteroarylcarbonyl, heterocyclocarbonyl or C_{1-6} alkylsulphonyl, provided that when R_5 is C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, arylsulphonyl, heteroarylsulphonyl, heterocyclosulphonyl, heteroarylcarbonyl, heterocyclocarbonyl, arylcarbonyl or C_{1-6} alkylsulphonyl, R_6 is not C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, arylsulphonyl, heteroarylsulphonyl, heterocyclosulphonyl, heteroarylcarbonyl, heterocyclocarbonyl, arylcarbonyl or C_{1-6} alkylsulphonyl ;

R_7 represents aryl, heteroaryl, heterocyclo or C_{1-6} alkyl, any of which may be optionally substituted with one or more substituents chosen from amongst halogen, aryl, heteroaryl, heterocyclo, C_{1-6} alkoxy, hydroxy, CO_2H, CO_2R_8, $SO_2NR_9R_{10}$, $CONR_9R_{10}$, NR_5R_6 or carbonyl oxygen;

R_8 represents C_{1-6} alkyl, arylalkyl, heteroarylalkyl or heterocycloalkyl;

R_9 and R_{10}, which may be the same or different, each represent H, aryl, heteroaryl, heterocyclo, C_{1-6} alkyl, arylalkyl, heteroarylalkyl, heterocycloalkyl;

R_{11} represents H, aryl, heteroaryl, heterocyclo, hydroxy, C_{1-6} alkoxy, arylalkyloxy, heteroarylalkyloxy, heterocycloalkyloxy, $-CO_2H$, CO_2R_8, $SO_2NR_9R_{10}$, $CONR_9R_{10}$, halogen, -CN, $-NR_5R_6$, COR_7, $S(O)_nR_7$, -CN or carbonyl oxygen;

m represents 1-2;

n represents 0-2

and pharmaceutically acceptable salts thereof, and, where applicable, all stereoisomers including enantiomers and diastereoisomers including racemic mixtures thereof.

2. A compound of claim 1, wherein R_3 is H, arylalkyl, heteroarylalkyl, heterocycloalkyl, COR_7, $S(O)_{0-2}R_7$ or alkyl optionally substituted by one or more of OH, alkoxy, COOH (or C_{1-6} alkyl ester or C_{1-6} alkyl amide thereof), NR_5R_6, CN, carbonyl oxygen, COR_7 and $S(O)_{0-2}R_7$;

R_4 is a 5 or 6 membered carboxylic or heterocyclic ring optionally substituted by one or more of aryl, heteroaryl, heterocyclo, carbonyl oxygen, OH, alkoxy, CN, COOH (or an ester or amide thereof), alkyl optionally substituted by OH, alkoxy, COOH (or an ester or amide thereof), NR_5R_6, CN, carbonyl oxygen, COR_7 or $S(O)_{0-2}R_7$, to which is fused a carboxylic or heterocyclic ring optionally substituted by one or more of halogen, aryl, heteroaryl, alkoxy, OH, COOH (or an ester or amide thereof), $S(O)_{0-2}R_8$, NR_5R_6 and alkyl optionally substituted by OH, alkoxy, COOH (or an ester or amide thereof), NR_5R_6, CN, carbonyl oxygen, COR_7 or $S(O)_{0-2}R_7$;

R_5 and R_6 are independently selected from H, alkyl, alkylcarbonyl, alkoxycarbonyl, arylsulphonyl, arylcarbonyl and alkylsulphonyl, or NR_5R_6 is a 5 or 6 membered heterocyclic ring, phthalimido, succinimido or maleimido;

R_7 is alkyl optionally substituted by one or more of halogen, aryl, heteroaryl, alkoxy, OH, NR_5R_6, $S(O)_{0-2}R_8$, carbonyl oxygen or COOH (or an ester or amide thereof); and

R_8 is alkyl, aryl or heteroaryl.

3. A compound of claim 1, wherein R_1 is alkyl or cycloalkyl, either being optionally substituted by halogen, alkoxy, aryloxy or arylalkoxy;

R_3 is H or alkyl optionally substituted by OH, alkoxy, COOH (or an ester or amide thereof), CN or carbonyl oxygen;

R_4 is a 5 or 6 membered carboxylic or heterocyclic ring, optionally substituted by carbonyl oxygen, OH, alkoxy, CN or COOH (or an ester or amide thereof), to which is fused a carboxylic or heterocyclic ring optionally substituted by halogen, alkoxy, OH, COOH (or an ester or amide thereof) or NR_5R_6; and

R_5 and R_6 are independently selected from H, alkyl, alkylcarbonyl, alkoxycarbonyl, arylsulphonyl, arylcarbonyl or alkylsulphonyl.

4. A compound of any preceding claim, wherein R_1 is alkyl optionally substituted by aryloxy, or cycloalkyl.

5. A compound of any preceding claim, wherein R_2 is methyl optionally substituted by halogen.

6. A compound of any preceding claim, wherein R_3 is H, arylalkyl, heteroarylalkyl, SO_2R_7 or C_{1-6} alkyl (optionally

substituted with one or more substituents chosen from hydroxy, $CONR_9R_{10}$, $SO_2NR_9R_{10}$, NR_5R_6, carbonyl oxygen, COR_7, SO_2R_7, CN, CO_2H or CO_2R_8).

7. A compound of any claim 1, selected from

N-(Indan-1-yl)-3,4-dimethoxybenzenesulphonamide,

N-(1,2,3,4-tetrahydronapth-1-yl)-3,4-dimethoxybenzenesulphonamide,

N-Cyanoethyl-N-(indan-1-yl)-3,4-dimethoxybenzenesulphonamide,

N-Cyanoethyl-N-(1,2,3,4-tetrahydronaphth-1-yl)-3,4-dimethoxy-benzenesulphonamide,

N-[1,2,3,4-Tetrahydro-6-acetamidonaphth-1-yl]-3,4-dimethoxybenzenesulphonamide,

N-[5-Acetamidoindan-1-yl]-3,4-dimethoxybenzenesulphonamide,

N-[5-Chloroindan-1-yl]-3,4-dimethoxybenzenesulphonamide,

N-[5-Methoxyindan-1-yl]-3,4 dimethoxybenzenesulphonamide.

8. A compound of claim 1, selected from

(R)-N-(Indan-1-yl)-3,4-dimethoxybenzenesulphonamide,

(S)-N-(Indan-1-yl)-3,4-dimethoxybenzenesulphonamide,

3,4-Dihydro-3S-(3,4-dimethoxybenzenesulphonamido)-2(1H)-quinolinone,

Methyl 3-(3,4-dimethoxybenzenesulphonamido)indane-1-carboxylate,

ethyl 3-((N-indan-1-yl)-3,4-dimethoxybenzenesulphonamido)propionate,

N-(5,6-Dimethoxyindan-1-yl)-3,4-dimethoxybenzenesulphonamide,

N-Indan-2-yl-3,4-dimethoxybenzenesulphonamide,

N-(4-Methoxyindan-1-yl)-3,4-dimethoxybenzenesulphonamide,

N-(6-Methoxyindan-1-yl)-3,4-dimethoxybenzenesulphonamide,

N-(5-bromoindan-1-yl)-3,4-dimethoxybenzenesulphonamide,

Methyl 1-(3,4-dimethoxybenzenesulphonamido)indane-2-carboxylate,

N-Indan-1-yl-N-(4-pyridylmethyl)-3,4-dimethoxybenzenesulphonamide,

N-Indan-1-yl-N-(3-pyridylmethyl)-3,4-dimethoxybenzenesulphonamide,

N-Indan-1-yl-N-(2-pyridylmethyl)-3,4-dimethoxybenzenesulphonamide,

N-(Indan-1-yl)-N-[4-(2-methylthiazolylmethyl)]-3,4-dimethoxy benzenesulphonamide,

N-(Indan-1-yl)-N-(methanesulphonyl)-3,4-dimethoxybenzenesulphonamide,

3-[(N-Indan-1-yl)-3,4-dimethoxybenzenesulphonamido]propanoic acid.

9. A compound of claim 1, selected from

N-(2-Hydroxyindan-1-yl)-3,4-dimethoxybenzenesulphonamide,

N-(Pyrindan-7-yl)-3,4-dimethoxybenzenesulphonamide.

10. A compound of claim 1, in the form of an enantiomer or diastereoisomer, or any mixture of either.

11. A pharmaceutical composition containing a compound according to any of claims 1 to 10 as active ingredient, in combination with suitable excipients.

12. A method for treating a disease state capable of being modulated by inhibiting production of phosphodiesterase IV, comprising administering to a patient suffering from said disease an effective amount of a compound according to any of claims 1 to 10.

13. The method of claim 12, wherein the disease state is a pathological condition associated with a function of phosphodiesterase IV, eosinophil accumulation or a function of the eosinophil.

14. The method of claim 13, wherein the pathological condition is selected from asthma, chronic bronchitis, atopic dermatitis, urticaria, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, inflammation of the eye, allergic responses in the eye, eosinophilic granuloma, psoriasis, rheumatoid arthritis, gouty arthritis and other arthritic conditions, ulcerative colitis, Crohn's disease, adult respiratory distress syndrome, diabetes insipidus, keratosis, atopic dermatitis, atopic eczema, cerebral

senility, multi-infarct dementia, senile dementia, memory impairment associated with Parkinson's disease, depression, cardiac arrest, stroke and intermittent claudication.

15. The method of claim 14, wherein the pathological condition is asthma.

16. A method for treating a disease state capable of being modulated by inhibiting TNF, comprising administering to a patient suffering from said disease an effective amount of a compound according to any of claims 1 to 10.

17. The method of claim 16, wherein the disease state is an inflammatory disease or autoimmune disease.

18. The method of claim 17, wherein the disease state is selected from joint inflammation, arthritis, rheumatoid arthritis, rheumatoid spondylitis and osteoarthritis, sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, acute respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoidosis, asthma, bone resorption diseases, reperfusion injury, graft vs host reaction, allograft rejection, fever and myalgias due to infection, such as influenza, malaria, myalgias, HIV, AIDS, ARC, cachexia, keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis, pyresis, systemic lupus erythematosus, multiple sclerosis, type 1 diabetes mellitus, psoriasis, Bechet's disease, anaphylactoid purpura nephritis, chronic glomerulonephritis, inflammatory bowel disease and leukaemia.

19. The method of claim 18, wherein the disease state is joint inflammation.

20. The method of claim 12 or claim 16, wherein the disease state is tardive dyskinesia.

21. The method of claim 16, wherein the disease state is a yeast or fungal infection.

22. A method for gastroprotection, comprising administering to a patient in need thereof an effective amount of a compound according to any of claims 1 to 10.

INTERNATIONAL SEARCH REPORT

Intc onal Application No
PCT/GB 96/01205

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C311/29 C07D215/38 C07D213/42 C07D277/28 C07D221/04
A61K31/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,94 02465 (RHONE-POULENC RORER) 3 February 1994 cited in the application see page 6 - page 7 ---	1,11-13
A	EP,A,0 306 846 (DR. KARL THOMAE) 15 March 1989 cited in the application see page 2 ---	1,11-13
A	EP,A,0 497 564 (RHONE-POULENC RORER) 5 August 1992 see page 2; claims -----	1,11-13

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 August 1996	21.08.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	English, R

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int. ational application No.
PCT/GB96/01205

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 12-22 are directed to a method of treatment of the human or animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

B x II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int onal Application No
PCT/GB 96/01205

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